Inverted follicular keratosis

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SYNOPSIS Attention is drawn to a benign skin tumour which has escaped recognition in the British literature. Inverted follicular keratosis can be mistaken clinically for basal cell carcinoma and a variety of benign skin lesions. Pathologically it is easily confused with squamous carcinoma, a serious error because this lesion occurs dominantly on the face. The lesion is thought to arise from the infundibulum of the hair follicle.

The purpose of this paper is to draw attention to a lesion which has been described in the dermatological and ophthalmic literature but which is little known to general pathologists. Helwig (1954) gave it the name 'inverted follicular keratosis' and described its essential characteristics. This description is, however, unavailable to most pathologists. Boniuk and Zimmerman (1963) reported on lesions of this type on the eyelids. We have not been able to find any reference to it in the British literature.

Materials and Methods

We collected nine lesions, all treated by surgical excision. Eight were found by searching our records between 1954 and 1973 inclusive, and one was seen

in consultation. Haemalum eosin sections were studied in all cases. In the eight cases from our own material, Best carmine, Masson-Fontana, Alcian green, and periodic acid Schiff stains were also studied. Step sections were examined in these eight cases.

CLINICAL DATA

All lesions were single, though one patient had a basal cell carcinoma at another site in addition. As can be seen from the table, eight lesions were situated on the face and one on the chest wall. Five lesions were situated on the cheek or upper lip. There were seven male and two female patients. All the patients were adults and, with the exception of a 36-year-old, aged 48 years or more. They presented mostly as asymptomatic papules and all were small lesions, measuring only a few millimetres in maximum diameter. They had a conical or dome-

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Case	Sex	Age	Site	Duration	Clinical Diagnosis	Follow-up	Original Pathological Diagnosis
1	M	57	Lower eyelid	2 mth	(Clinical notes lost)	Well 18 yr	Squamous carcinoma or keratoacanthoma
2	F	55	Cheek		Rodent ? Kerato-acanthoma		
3	M	60	Upper lip	6 mth	? Rodent Squamous carcinoma	Well 8 yr	IFK
4	M	53	Cheek	6 mth	—	Well 10 yr	IFK
5	M	49	Upper lip	10 mth	—	Lost	IFK
6	M	52	Chest	'Many years' with recent increase in size	? 'Cutaneous horn'	Well 7 $\frac{1}{2}$ yr	IFK
7	M	36	Cheek	2 yr	—	Well 6 $\frac{1}{2}$ yr	IFK
8	M	48	Temple	3 mth	—	Well 2 $\frac{1}{2}$ yr	IFK
9	F	74	Nose	10 mth	? Rodent	Well 1 yr	IFK

Table Summary of clinicopathological data on cases

IFK = inverted follicular keratosis

Fig 1 Low-power view of mainly protuberant lesion. Note that part of lesion extends downwards into the dermis. Haematoxylin and eosin $\times 23$

Fig 2 Low-power view of mainly 'inverted' lesion. H and E $\times 23$

shaped elevation. They were pinkish or flesh-coloured and not obviously pigmented.

PATHOLOGY

The low-power appearance varies between a lesion that protrudes mainly outwards to a more common one which grows predominantly inwards into the corium (figs 1 and 2). Even when a lesion grows dominantly outwards, part of it is inward-growing so that the entire tumour is not raised above the level of the surrounding skin surface (fig 1). The surface varies between papillomatous in the more protuberant, and more-or-less convex in the dominantly ingrowing lesion. There is hyperkeratosis, parakeratosis or both superficially. The lesion is generally well demarcated, with usually sharp inversion of the epidermis on one or both edges. It may therefore have a cup-shaped structure with a geographical, though not a cytological, resemblance to keratoacanthoma.

It has an essentially lobular configuration with blunt outlines (fig 2). There is no raggedness at the epithelial-stromal junction (fig 3). The lobules may be largely separate, compressing the stroma between them, or they may merge together at varying levels, causing apparent isolation of areas of stroma within the epithelial mass (fig 4). Hair follicles enter the lesion on the deep aspect and lose their identity within it.

The lobules contain a more-or-less central longitudinal crypt (fig 1). This contains keratin and is lined by squamous epithelium usually with, but sometimes without, a granular layer. The crypt may open on the surface, and its contents are then continuous with the keratinous scale there: in a

Fig 3 *Sharply demarcated laterally, the lesion is expansile and has a blunt lobular configuration. H and E $\times$ 45*

given plane of section, the crypt may be elliptical and appear isolated from the surface. Sebaceous glands are attached to the deep margins of the lobules in at least four of the eight cases examined by step sectioning (fig 5). In addition, in one of the four cases, hair shafts are present in two crypts. This strongly suggests that the lobules represent a pro-

liferation of the external sheath of hair follicles and that the infundibular portion of the follicle is primarily involved in the process.

The cytology is in part basaloid and in part squamous. The relationship of the two cell types constitutes an essential and characteristic feature. Basaloid cells are more numerous at the periphery

Fig 4 *Two adjacent tumour lobules with compressed stroma, apparently isolated between them, running diagonally above centre. H and E $\times$ 110*

Fig 5 Sebaceous gland remnants incorporated within the deep part of the lesion. *H and E* $\times 275$

of the lobules, and squamous cells towards the centre of the lobules and around the keratin-filled crypts. While basaloid cells sometimes merge with squamous cells indefinitely, it is at the points of junction of these two cell types that the so-called 'squamous eddy' is frequently found (figs 4 and 6). This consists of a sharply demarcated, rounded

group of larger, eosinophilic, polygonal cells set in a background of basaloid cells. The cells of the eddy have an orderly arrangement, lack pleomorphism, and are virtually never in mitosis. Occasionally keratohyaline granules are present in the centre of the eddy and, less commonly, a very small focus of keratin. A very rare cell may even

Fig 6 Numerous characteristic squamous eddies with uniform squamous cells lacking cytological atypia. *H and E* $\times 275$

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show individual-cell keratinization. Keratohyaline granules in a squamous eddy are sometimes numerous and coarse, reminiscent of those seen in viral warts, though no aetiological relationship is implied: in such areas there is usually a prominent thick granular layer in the lining of the crypts. There is an overall organized arrangement about the concentrically laminated eddies that distinguishes them fairly easily from the epithelial pearls of squamous carcinoma. Squamous eddies vary in number in different lesions and different parts of the same lesion. They are, however, such a characteristic feature that it is very doubtful if one can diagnose this entity in their absence. They tend to be most numerous in the centres of the epithelial masses. Where they are very numerous, they abut on one another without becoming confluent.

The basaloid cells are small, haematoxyphilic, immature cells. Mitoses are seen in them, as many as three per high-power field being present in some areas. This degree of proliferative activity adds to the tendency to misdiagnose some of the lesions as malignant. No abnormal mitoses are present. Mitoses are found only occasionally in the squamous cells (and may even be numerous in the superficial part of the lesion) but are very rarely seen in the cells constituting the eddy.

Another characteristic, but not essential, feature is the clefting that occurs within the epithelial masses (figs 3 and 7). This is most conspicuous close to

the surface of the lesion, around the crypts, and between some contiguous squamous eddies: occasionally it is seen also at the junction of the eddy and the basaloid cells. Where clefting is pronounced, microvesicles are found within the epithelium. While these clefts are doubtless in part artefact, it is unlikely that they are entirely so, since Alcian-green-stainable mucinous material is frequently present in the crevices.

Melanin pigmentation is usually conspicuous by its absence in haemalum-eosin preparations. In eight lesions no melanin is visible in haemalum-eosin sections; in one a very little melanin is visible in stromal macrophages on very careful scrutiny. With Masson-Fontana staining, variable numbers of melanocytes are present in all eight lesions with available material. Melanocytes are patchily distributed among the basaloid cells. Similarly, melanin pigment is present in some of the areas composed of basaloid cells.

The epithelial-stromal junction is sharply defined (figs 2 and 3). The dermis shows increased vascularity, with occasional telangiectatic vessels superficially. Inflammatory cells vary from an inconspicuous to a moderately dense infiltrate with lymphocytes and histiocytes the dominant cells. Plasma cells are conspicuous in only two of the nine cases, including one with a purulent scab on the surface. Eosinophils are usually scarce and neutrophils absent. The dermal inflammatory cells sometimes

Fig 7 Clefting between contiguous squamous eddies. *H and E* $\times 275$

extend into the epithelial masses though the invasion is not usually widespread. Microabscesses are not a feature.

Discussion

Inverted follicular keratosis is almost always a solitary lesion, occurring mainly in adult life. The average age in Mehregan's series (1964) was 50 years. The youngest patients in Boniuk and Zimmerman's (1963), Mehregan's (1964), and our series were 17, 25, and 36 years respectively. Men are affected about twice as often as women. About 85% of these lesions are found on the face. The cheek and upper lip are the sites of predilection, other sites affected being the chin, forehead, eyebrow, nose, and eyelid. Upper or lower lids may be involved, lesions having a predilection for the lid margins. It is important, in this context, to remember that squamous carcinoma of the lid margins is excessively rare. The trunk is involved uncommonly and the extremities rarely. The duration of the lesion, when known, has varied between six weeks and three years. One patient of Duperrat and Mascaro (1963) had a seven-year history. Most of the lesions are between 3 and 8 mm in maximum diameter, but a few reach a size of 10 mm. They are generally asymptomatic, firm, pinkish papules. Rarely they present as 'cutaneous horns'. Clinically they are often considered to be viral warts, the remainder being diagnosed as basal cell carcinoma or a variety of benign lesions (Mehregan, 1964). Basal cell carcinoma was the favoured clinical diagnosis in at least three of our cases.

Pathologically, they pose very real diagnostic problems unless one is aware of this entity. They can be confused with a variety of lesions, both benign and malignant. Our oldest case was considered to be a squamous carcinoma of the eyelid and the next oldest either a squamous carcinoma or a keratoacanthoma, with the latter diagnosis favoured. The later cases were diagnosed as inverted follicular keratosis following Helwig's (1954) account.

The most difficult differential diagnosis is from a seborrhoeic keratosis of the variety described as 'irritated'. Such a lesion, whether spontaneously occurring or experimentally produced (Morales and Hu, 1965; Mevorah and Mishima, 1965), may contain squamous eddies in abundance. Clefting has also been noted by us in irritated seborrhoeic keratosis. We agree with Lever (1967) that the basosquamous acanthoma of Lund (1957) is a variant of seborrhoeic keratosis. However, we regard inverted follicular keratosis as a distinct entity, though not excluding the possibility of patho-

genetic kinship. Seborrhoeic keratosis usually contains horny invaginations, many of which are unrelated to hair follicles. Melanin pigmentation is often more prominent. But the most important distinction is the microanatomy: seborrhoeic keratosis is, and remains, raised above the level of the surrounding skin, even when it is situated over a pressure point. By contrast, inverted follicular keratosis has a downward growing component, usually dominant but always present to a slight degree at least. Because in the final analysis this is the most important single distinguishing feature, the differential diagnosis may be impossible on a small biopsy or a badly orientated specimen. Fortunately the distinction in such cases is academic.

Keratoacanthoma can be distinguished with relative ease (fig 2). Though many of the lesions here described have a cup-like structure, they lack the ballooned pale-staining squamous epithelium and the infiltrative pattern of the deep edge of keratoacanthoma and have a lobular growth pattern and characteristic squamous eddies instead.

Viral warts and other benign lesions do not constitute a difficult problem in differential diagnosis to the pathologist, despite the clinical similarity.

Squamous carcinoma is the most serious differential diagnosis, because it is not infrequently considered or made on pathological grounds in patients with this condition. This can lead to unnecessarily drastic treatment of a benign lesion. Inverted follicular keratosis has a lobular blunt-edged architecture and lacks the frayed, jagged, infiltrative margin of squamous carcinoma. The lateral edges are sharp, while in squamous carcinoma there is frequently a transition to abnormal epidermis which is not overtly malignant. The two main cell types present have an orderly arrangement. The squamous eddies have a monotonous uniformity that distinguishes them from epithelial pearls (figs 4, 6, and 7). Abnormal mitoses are not found in inverted follicular keratosis. The nuclear and cytological pleomorphism of squamous carcinoma is lacking.

The pathogenesis of these lesions is debatable. The name 'inverted follicular keratosis' has the merit of being generally descriptively accurate and of suggesting a follicular origin. It is true that some of the lesions are dominantly superficial, and the designation 'inverted' is not wholly applicable. Nevertheless, for the present, it seems desirable to retain this name. Boniuk and Zimmerman (1963) suggested the possibility of a viral aetiology. Duperrat and Mascaro (1963) were the first to suggest origin specifically from the infundibulum of the hair follicle, and Mehregan (1964) strongly supports this hypothesis, which has much to

commend it. The alternative names follicular poroma (by analogy with eccrine poroma) or infundibuloma, that have been suggested, might be appropriate if this histogenetic view became generally accepted.

If one separates the irritated seborrhoeic keratosis (basosquamous acanthoma), there is no doubt that inverted follicular keratosis is an uncommon condition. It deserves more general recognition especially because of the ease with which the pathologist, unfamiliar with the condition, can make an erroneous diagnosis of squamous carcinoma. The seriousness of this error will be appreciated when it is remembered that about 85% of these lesions are situated on the face. An erroneous diagnosis of basal cell carcinoma may be made instead, though this error is much less frequent. One of us has seen a case (not included in this series) diagnosed as basisquamous carcinoma. A diagnosis of basisquamous carcinoma is nowadays viewed with some scepticism. The more widespread recognition of inverted follicular keratosis as an entity will add to the legitimate doubt as to the existence of a lesion that deserves to be classified as basisquamous carcinoma.

A diagnosis of inverted follicular keratosis carries an excellent prognosis. Boniuk and Zimmerman (1963) studied 28 patients with a follow-up period of five years or more. No deaths were attributable to the tumour. Follow-up was available in a total of 46 patients: a single patient had a local recurrence following cautery excision. No follow-up was possible in two of our patients. The remaining seven are well

without recurrence at 1, 2 $\frac{4}{12}$, 6 $\frac{5}{12}$, 7 $\frac{7}{12}$, 8, 10, and 18 years respectively.

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References

- Boniuk, M. and Zimmerman L. E. (1963). Eyelid tumors with reference to lesions confused with squamous cell carcinoma. II. Inverted follicular keratosis. *Arch. Ophthalm.*, **69**, 698-707.
- Duperrat, B. and Mascaro, J. M. (1963). Une tumeur bénigne développée aux dépens de l'acrotrichium ou partie intraépidermique du follicule pileux: porome folliculaire. *Dermatologica (Basel)*, **126**, 291-310.
- Helwig, E. B. (1954). Seminar on the skin: neoplasms and dermatoses. *Proceedings of the 20th Seminar of the American Society of Clinical Pathologists, International Congress of Clinical Pathology, Washington, D.C.*
- Lever, W. F. (1967). *Histopathology of the Skin*, 4th edition, p. 490. Lippincott Philadelphia: Pitman, London.
- Lund, H. Z. (1957). *Tumors of the Skin*. (Atlas of Tumor Pathology, Section 1, Fascicle 2), p. 42. Armed Forces Institute of Pathology, Washington, D.C.
- Mehregan, A. H. (1964). Inverted follicular keratosis. *Arch. Derm.*, **89**, 229-235.
- Mevorah, B. and Mishima, Y. (1965). Cellular response of seborrhoeic keratosis following croton oil irritation and surgical trauma. *Dermatologica (Basel)*, **131**, 452-464.
- Morales, A. and Hu, F. (1965). Seborrhoeic verruca and intraepidermal basal cell epithelioma of Jadassohn. *Arch. Derm.*, **91**, 342-344.